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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/882,509	06/15/2001	Mosuvan Kuppusamy	51321-003	8339

25005 7590 06/13/2005  
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EXAMINER

MONSHIPOURI, MARYAM

ART UNIT PAPER NUMBER

1652

DATE MAILED: 06/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	09/882,509	KUPPUSAMY ET AL.	
	Examiner	Art Unit	
	Maryam Monshipouri	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is FINAL.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 8-11 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-5 and 8-11 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |  |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. <u>march 05</u> |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)                                  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____  |

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Applicant's response to advisory action filed 4/18/2005 is acknowledged and is hereby entered. Claims 1-5 and 8-11 are still pending. Claims 6-7, 12-21 are canceled. Applicants' arguments filed on 4/18/2005 also have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

In view of applicant's arguments the finality of the office action dated 12/15/2004 is hereby withdrawn. An office action on the merits is drafted as following:

**Supplemental Detailed Action**

Claims 1-5 and 8-11 are under examination.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "enzymatically-active" in claims 1 (and its dependent claims 2-3), claim 4 (and its dependent claims 5-10) and claim 11 is unclear and misleading. The specification teaches steps of solubilization and purification and renaturation of streptokinase prepared in inclusion bodies (see pages 11-13), which results in activation of the enzyme (as applicant is well aware, before an enzyme is solubilized it is inactive). The specification nowhere displays any SKC activity

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in inclusion bodies. However, the phrase as currently recited, appears to imply that the streptokinase in inclusion bodies is already active. Appropriate clarification is required.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Pupo (cited previously) according to previous office actions. In traversal of this rejection applicant argues the following: (1) that Pupo never said the SKC activity present in the “insoluble faction” was itself insoluble. Pupo wrote (see page 1122) that “the low amount of SKC in the insoluble faction” was caused by contamination with “soluble SKC”. According to applicant, Pupo’s “insoluble faction” did not contain “insoluble SKC” as alleged by the Office. Pupo’s insoluble faction was only contaminated with soluble SKC. Pupo also fails to indicate that SKC activity found in the insoluble faction is “insoluble”. Therefore the examiners’ conclusion that SKC activity remaining in the insoluble faction is therefore “insoluble”, is not supported by the clear language of Pupo.

In view of applicant had Pupo been a little more careful in separating the soluble fraction from the insoluble fraction, the contamination would not have been happened in the first place. And Pupo’s insoluble fraction would have been devoid of SKC activity.

(2) Pupo does not teach anything regarding making insoluble and enzymatically active streptokinase. They only teach that one should be careful in separating the soluble from the insoluble fractions so as not to cause cross-contamination. Pupo do not enable the public to fabricate insoluble SKC in the form of an enzymatically active inclusion body. Pupo merely shows in Fig. 2, lane 6, that the insoluble cell fragment may be contaminated by soluble SKC.

Therefore in view of these arguments the rejection should be withdrawn. These arguments, which are basically the same as previously presented, were fully considered but again were found **unpersuasive** for the following reasons: with respect to applicant's **first** argument the examiner maintains that Pupo does not need to explicitly say that the "insoluble faction" is insoluble SKC. Any one of ordinary skill in the art is fully aware that once one prepares a recombinant enzyme (in this case being SKC) in inclusion bodies most (if not all) of said enzyme is in insoluble form. Further, as already indicated above, when an enzyme is insoluble it is inherently devoid of activity. Enzyme activity only appears when enzyme is soluble. Therefore applicant's argument that Pupo fails to indicate that SKC activity in the insoluble fraction is insoluble SKC does not make sense. The examiner is puzzled as to why applicant keep raising the fact that insoluble SKC of Pupo had some contamination of soluble SKC, which could be washed off with PBS. It is totally unclear as to how such argument can help applicant overcome the art.

As mentioned previously, Pupo is merely cited to indicate that SKC preparation in inclusion bodies has been done prior to this invention. The method used to remove

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contamination from said (insoluble) SKC and what Pupo should have done to avoid contamination are totally irrelevant.

In response to applicant's **second** argument it should be noted that the terms "enzymatically active" and insoluble" are contradictory to each other. This is because for an enzyme to be active it must be soluble. Therefore, it is not surprising than Pupo did not teach insoluble, enzymatically active SKC.

Further, applicant is respectfully requested to note the 112 second rejection drafted above. As already mentioned applicant himself/herself does not disclose the preparation of "enzymatically active inclusion bodies". The SKC prepared in inclusion bodies of this invention was solubilized, denatured and purified for activation. Hence, the examiner is of the opinion that may be applicant needs to read the details of the invention, more carefully, before commenting on Pupo's enablement issues as he/she himself/herself keep stressing on a point, namely insoluble but enzymatically active SKC, which has not been enabled in the specification.

Therefore, due to the response provided above, in addition to responses and discussions provided previously the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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Claims 2, 4-5, 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pupo (cited previously) in view of Schmitz (U.S. Patent No. 5,708,148, issued 1/13/1998). As mentioned previously Pupo teaches methods of producing streptokinase using a DNA expression construct (see vector pACS0-2, page 1120) comprising the streptokinase (sck-2) gene from *S. equisimilis* (ATCC 9542), which inherently has SEQ ID NO:3, because it originates from the same source as SEQ ID NO:3 and inherently drives formation of inclusion bodies comprising "enzymatically active" (see rejection above) streptokinase, whereby the host cell expresses inclusion bodies comprising "enzymatically active" streptokinase (see Figure 2). Pupo neither teaches a DNA expression construct wherein the promoter is  $\lambda$ pL nor teaches heat inducing the host cell for expression of insoluble SKC comprised in inclusion bodies.

Schmitz teaches (see column 5) a process for recombinant production of recombinant IGF-II in inclusion bodies as well a processes for isolation and refolding of said protein in its biologically active form (see abstract and claims). Schmitz (in column 5-6) specifically teaches that for example, thermolabile  $\lambda$ CI<sub>857</sub> repressor may be used for heat induction of a hybrid vector comprised in a host cell (e.g. *E. coli*) comprising a gene encoding its IGF-II at 42 °C for 10h.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to art with the DNA construct of Pupo and insert one of the promoters of Schmitz (such as  $\lambda$ N,  $\lambda$ pL,  $\lambda$  CI<sub>857</sub> , or mutants thereof etc.) in order to be able to induce expression of the SKC of Pupo by heat, according to the method of Schmitz. One of ordinary skill in the art is motivated in utilizing heat in inducing

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expression of Pupo's SKC comprised in inclusion bodies because heat is a more economical and more convenient induces than chemicals such as antibiotics for recombinant expression of proteins and enzymes.

Finally, one of ordinary skill in the art is motivated in inserting the thermolabile promoters (repressors) of schmitz into the expression construct of Pupo for recombinant expression of SKC in inclusion bodies according to the method of Schmitz, because Schmitz has successfully used said promoters for heat induction of recombinant IGF-II in inclusion bodies, rendering the invention obvious.

**No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maryam Monshipouri whose telephone number is (571) 272-0932. The examiner can normally be reached on 7:00 a.m to 4:30 p.m. except for Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnanthapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306 or (571)273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair->

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Maryam Monshipouri Ph.D.

Primary Examiner

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